IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Davis, et al.
App. No	:	10/809,975
Filed	:	March 26, 2004
For	:	MUSCARINIC M1 RECEPTOR AGONISTS FOR PAIN MANAGEMENT
Examiner	:	Umamaheswari Ramachandran
Art Unit	:	1617

DECLARATION OF DOUGLAS W. BONHAUS UNDER 37 C.F.R §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Douglas W. Bonhaus declare and state that:

1. I am Vice President, Biosciences of Acadia Pharmaceuticals Inc., current assignee of the instant application.

2. I received my Ph.D. in Pharmacology and Toxicology in 1983 from the University of Arizona. After post doctoral training and then serving as Research Assistant Professor in the Neurology Division of the Department of Medicine at Duke University, I joined the pharmaceutical company Syntex in 1991 as a research scientist. In 1995, Syntex was aquired by Roche and I continued at Roche Biosciences as a principal scientist and then Senior scientist until 2005. In 2005, I joined Acadia Pharmaceuticals as vice president of Biosciences. Thus in addition to academic training, I have over 17 years experience in drug discovery and development, particularly in the fields of neuropsychiatric disorders, neuropathic pain, and migraine. I have published several papers in peer-reviewed journals.

3. I am familiar with the specification and prosecution history of U.S. Patent Application Serial No. 10/809,975, and the outstanding Office Action.

4. I describe herein several experiments that were conducted in the department of biosciences at Acadia Pharmaceuticals. Some of these experiments were conduced under my direction. Others were conducted prior to my arrival at Acadia. However, I have a full understanding of all experiments described herein. These experiments follow the teachings provided in the specification and provide additional examples of the claimed invention. These experiments demonstrate the operability of the invention and that the specification provides sufficient instruction such that one skilled in the art could successfully generate working examples without undue experimentation.

R-SAT assay to identify M(1) selective compounds

5. In one set of experiments, an R-SAT assay was used to identify compounds selective for the M(1) receptor subtype. The potency and efficacy of five compounds, labeled herein as Compounds 1-4, were measured using an R-SAT assay in a manner similar to that described in Example 1 of the instant application. The results of the R-SAT assay are presented in Table 1.

Table 1

Compound	**M1 potency (pEC50) and efficacy (%)**	**M2 potency (pEC50) and efficacy (%)**
1	7.7 (117)	6.4 (80)
2	7.5 (125)	6.0 (109)
3	7.1 (111)	5.9 (103)
4	7.2 (76)	Inactive

6. The results presented in Table 1 demonstrate that Compounds 1-4 are selective for the M(1) receptor subtype. Accordingly, Table 1 demonstrates that using an R-SAT assay in a manner similar to that described in Example 1 of U.S. Patent Application No. 10/809,975, additional compounds selective for the M(1) receptor subtype can be readily identified and selected without undue experimentation by one skilled in the art.

Sciatic nerve lesion assay for anti-neuropathic pain activity

7. In a related set of experiments, a sciatic nerve lesion model for neuropathic pain was used to measure the anti-neuropathic pain properties of Compounds 1-4. The model used was similar to that described in Example 3 of U.S. Patent Application No. 10/809,975. Transgenic mice lacking the M(1) receptor subtype and wildtype mice were administered Compounds 1-4. Such transgenic mice are described in Example 3 of U.S. Patent Application No. 10/809,975. The results are presented in Figures 1-7.

8. Results for Wildtype mice. Figures 1, 2, 4, and 6 illustrate the anti-neuropathic pain effects in wildtype mice of Compounds 1, 2, 3, and 4, respectively. Controls are shown in Figures 1 and 2 with mice that have not undergone partial sciatic ligation surgery (PSLS; also known as Partial Sciatic Nerve Ligation - PSNL) (open circles); and mice that have undergone PSLS but are administered vehicle only (open boxes). As expected, mice that have not undergone PSLS maintain a high paw withdrawal threshold. Conversely, mice that have undergone PSLS but are administered vehicle only (open boxes) have a low paw withdrawal threshold.

9. With respect to test compounds, Figures 1, 2, 4, and 6 show that mice that have undergone PSLS and are administered a test compound (indicated as "TC" in the figures - triplicate experiments with differing doses: closed circles; open triangles; closed boxes) have an increased paw withdrawal threshold. Thus, each test compound has anti-neuropathic pain activity in wildtype mice. The results of Figures 1, 2, 4, and 6 further demonstrate that selecting M(1) receptor agonists are effective at treating neuropathic pain and that one skilled in the art using an assay similar to the sciatic nerve lesion model for neuropathic pain disclosed in the specification of U.S. Patent Application No. 10/809,975, can readily verify that such compounds are useful to treat neuropathic pain without undue experimentation.

10. Results for Transgenic mice. Figures 3, 5, and 7 illustrate the lack of anti-neuropathic pain activity for Compounds 2, 3, and 4, respectively, in transgenic mice lacking the M(1) receptor subtype. A control is shown in Figure 5, where wildtype mice administered with Compound 3 (open circles) show an increase in paw withdrawal threshold.

11. With respect to test compounds, Figures 3, 5, and 7 show that transgenic mice that have undergone PSLS and administered with a test compound (triplicate experiments with differing doses: closed circles; open triangle; closed boxes) have a low paw withdrawal

threshold. Thus, the results of Figure 3, 5, and 7 further demonstrate that Compounds 2, 3, and 4 act through the M(1) receptor subtype to treat neuropathic pain.

Tail flick assay for anti-acute pain activity

12. In another set of related experiments, a tail flick assay similar to the assay described in U.S. Patent Application No. 10/809,975 under the heading 'Acute Thermal Analgesia' of Example 1 was used to measure the anti-acute pain activities of Compounds 1-4. These studies were conducted by immersing the tail of a rodent in water warmed to 55 °C. An animal with normal acute pain responses will withdraw its tail from the water within 1-2 seconds. However, an animal with impaired acute nociception will have a delayed response. Compounds 1-4 showed no activity using the tail flick assay. In other words, Compounds 1-4 do not have anti-acute pain activity. These results show that one skilled in the art using a tail flick assay similar to the assay disclosed in the specification of U.S. Patent Application No. 10/809,975 can readily verify that selective M(1) agonists alleviate neuropathic pain without alleviating acute pain without undue experimentation.

13. Taken together, these results demonstrate that the specification of U.S. Patent Application No. 10/809,975 provides information sufficient for one or ordinary skill in the art to identify and select compounds that are selective for the M(1) receptor subtype and can be used to treat neuropathic pain without alleviating acute pain without undue experimentation. The results also demonstrate that selective M(1) agonism is predictive for efficacy against neuropathic pain while not alleviating acute pain.

14. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States codes and that such willful, false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: Aug 21 2008 By: Doug Bonhaus
Douglas W. Bonhaus, Ph.D.

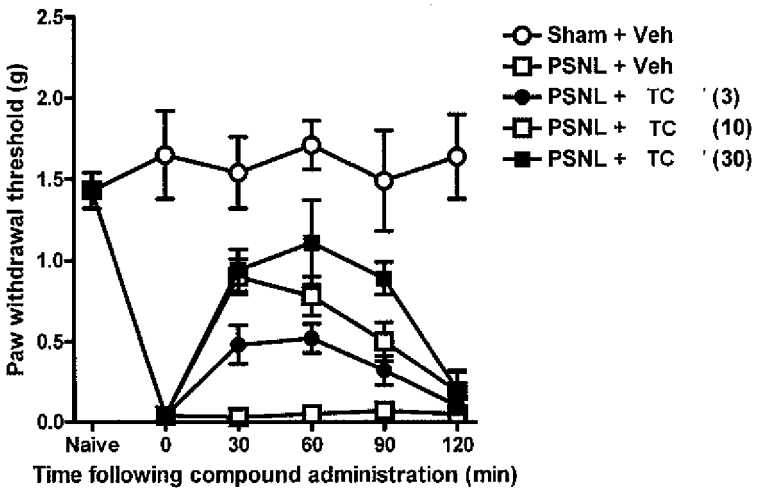

Figure 1

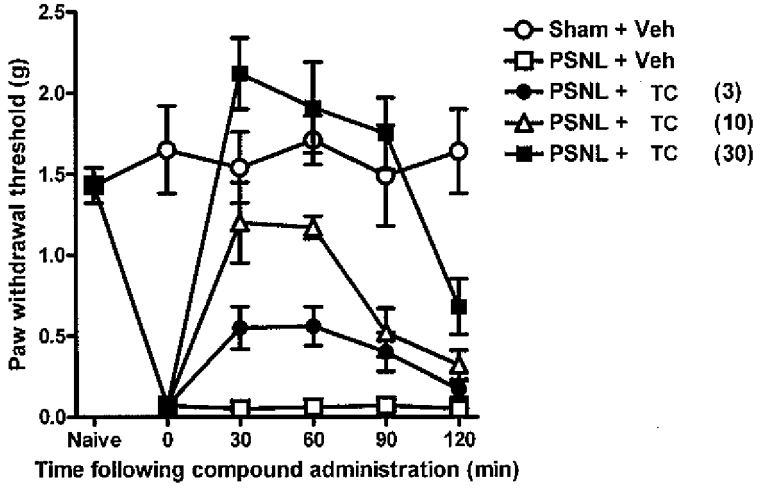

Figure 2

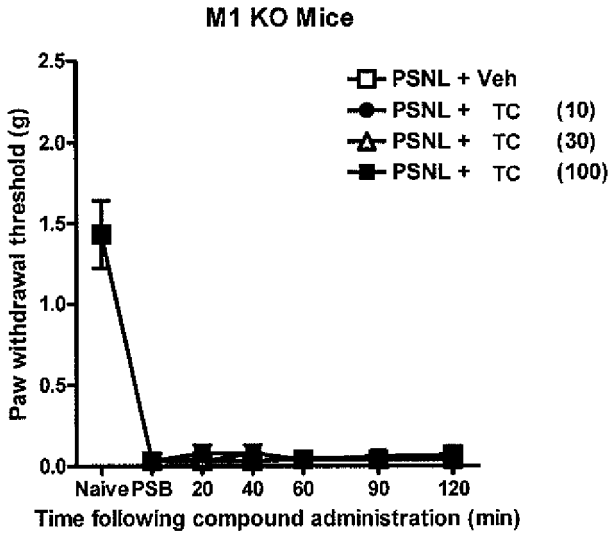

Figure 3

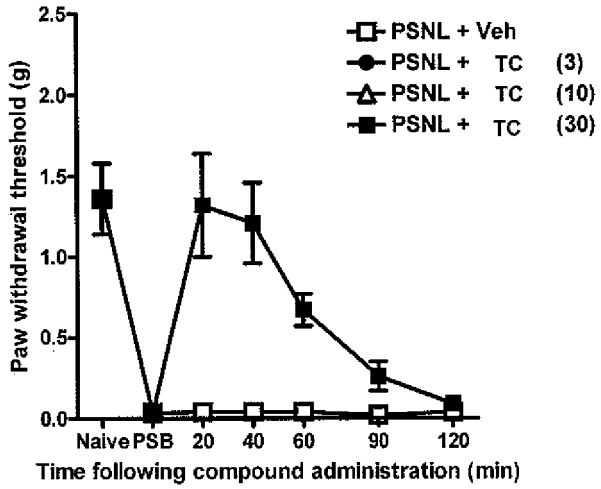

Figure 4

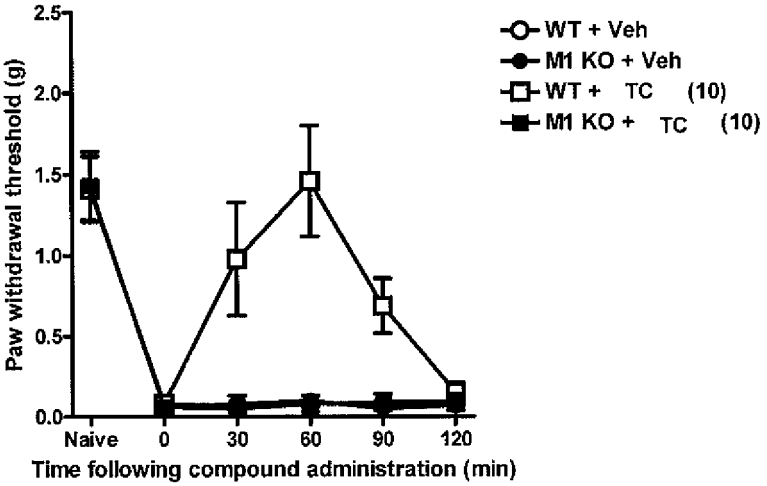

Figure 5

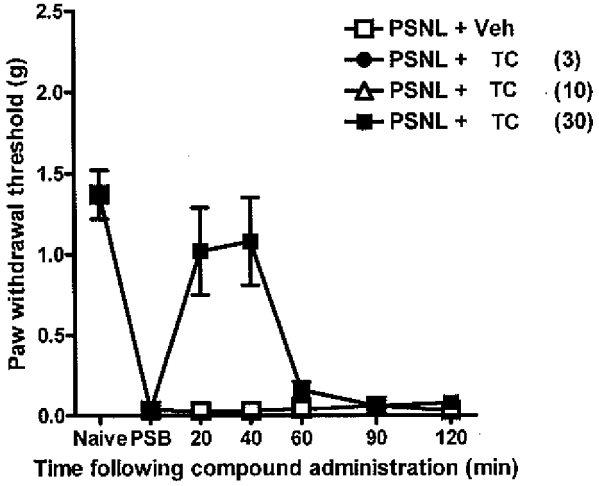

Figure 6

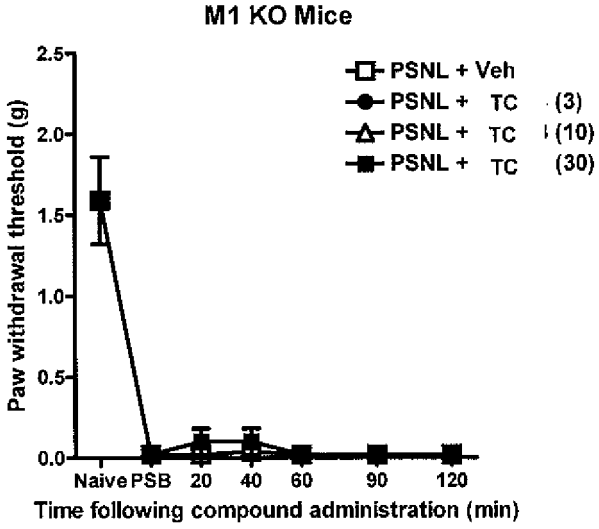
M1 KO Mice
PSNL + Veh
PSNL + TC (3)
PSNL + TC (10)
PSNL + TC (30)
Paw withdrawal threshold (g)
2.5
2.0
1.5
1.0
0.5
0.0
Naive PSB 20 40 60 90 120
Time following compound administration (min)

Figure 7